CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

MSMA and MAA
(Monosodium methanearsonate and free acid)
SB 950-076, Tolerance # 289
Chemical code #: 000034
August 11, 1986
Revised 6/2/87, 3/13/89, 2/23/91

I. DATA GAP STATUS

Combined rat: (chronic + onco.)	No data gap, possible adverse effect
Chronic dog:	No data gap, no adverse effect
Onco mouse:	Data gap, no study on file, study in progress
Repro rat:	Data gap, inadequate study, no adverse effect indicated
Terato rat:	No data gap, no adverse effect
Terato rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome:	No data gap, no adverse effect

DNA damage: No data gap, no adverse effect

Neurotox: Not required at this time

----------**Note, Toxicology one-liners are attached**

** indicates acceptable study
Bold face indicates possible adverse effect
File name T910223
Toxicology Summary prepared by J. Gee
Revised: Kishiyama, 12/27/88; Gee, 3/3/89; Kishiyama & Silva, 2/23/91.
Grouped with disodium methanearsonic acid (DSMA), tolerance # 50473, SB950 # 058
Rectified with the CDFA Library printout through volume 044, Record # 091665.

II. TOXICOLOGY ONE-LINERS AND DISCUSSION

COMBINED (CHRONIC + ONCO) RAT

** **044 091665**, "Combined Chronic Feeding and Oncogenicity Study in the Rat", (S. Crown, A. Nyska, T. Waner, Life Science Research Israel Ltd., LSRI Project No. PAL/004/MAA, 7/18/90). Methanearsonic acid (MAA, purity = 98.4 - 98.8%, Lot #: 107/84) was administered in feed at concentrations of 0 (untreated), 50, 400, or 1300 ppm to 60 Fischer rats/sex/group for 2 years. The 1300 ppm dosage was reduced (US EPA approval) to 1000 ppm during week 53 and further reduced to 800 ppm during week 60 due to mortality. CHRONIC NOEL = 50 ppm/day (Reduced body weight with increased food consumption was observed in both sexes at the high dose. Increased water consumption and diarrhea were observed at $\geq$ 400 ppm in both sexes. The pH of urine in males at 24 months was significantly decreased at the high dose throughout the study. Liver and kidney weights in females (% bodyweight) increased at $\geq$ 400 ppm (with accompanying clinical chemistry). Pathological changes, accompanied by histopathology were observed in the large intestine (cecum, rectum, colon) and in the thryoid at $\geq$ 400 ppm in both sexes.) ONCOGENICITY NOEL = 50 ppm/day (Parathyroid adenomas were observed at an increased rate in males at $\geq$ 400 ppm and in females at the high dose. Clinical chemistry effects on calcium (females) and phosphorous (males) support these findings.) ACCEPTABLE. (Kishiyama & Silva, 1/25/91).

CHRONIC, DOG

** 289- 036 066379, "Methanearsonic Acid: Fifty Two Week Chronic Oral Study in Beagle Dogs", (Life Science Research Israel Ltd., Israel; LSRI Report No. PAL/008/MAA, January 25, 1988). Methanearsonic acid technical (MAA), purity 99.8%, was administered by oral capsule at doses of 0 (empty capsule), 2, 8, and 35 mg/kg/day to 5 beagle dogs/sex/group for 52 weeks. Body weight gain was depressed in high and mid-dose female groups. Increased incidence of vomiting

in female and male high-dose groups; excessive salivation and diarrhea in mid and high-dose males and females was reported. Systemic NOEL = 2 mg/kg/day (clinical signs, decreased weight gain). Other reported effects of MAA were considered non specific. No adverse effect. ACCEPTABLE. (Kishiyama & Gee, 3/1/89)

ONCOGENICITY, RAT

289- 014 011334 (1975) Review, no data. See above.

ONCOGENICITY, MOUSE

A 78-week study is in progress at Life Science Research, Israel. The main study was initiated in February, 1986 but due to excessive mortality was terminated and a new study initiated in October, 1987.

289- 035 (2 parts) 066053 "Methanearsonic Acid - Chronic Feeding Study in the Mouse." (Life Science Research Israel, PAL/022/MAA, 11/3/87) Methanearsonic acid, technical, batch 107/84, >99.8%; fed in the diet to B6C3F1 mice at 0, 300, 1100, 2500 decreased to 1800 at week 18, or 4000 ppm decreased to 1800 ppm at week 18; doses were decreased due to high mortality from toxicity of MAA; 56/sex/group; study was terminated at week 42 - 46; major findings were in the gastrointestinal tract including clinical signs of diarrhea, soft or mucoid feces and supported by microscopic findings of cuboidal to squamous metaplasia of epithelial columnar absorptive cells, especially in males with incidences at all dose levels; additional clinical signs were hunching and tremors at 1100 ppm and higher; NOEL < 300 ppm (GI tract findings and decreased weight gain). SUPPLEMENTARY (length of study). (Gee, 3/1/89.)

REPRODUCTION, RATS

289- 017-022 041669-041674 "Methane Arsonic Acid: Three Generation Reproduction Study in Rats." (11/26/1979, Raltech (WARF)) MSMA as free acid (MAA), lot 907-96-301, >99%; fed in the diet at 0, 25, 50, 100 or 200 ppm to 40/sex/group for three generations, 2 litters each; NOEL $\geq$ 200 ppm; no adverse effect on reproduction reported. Deficiencies include no adequate justification of dose, no analyses of diet for content or stability or mixing homogeneity, no individual body weights and food consumption or clinical observations. Gross necropsy on F1b high dose only and not F0. No signs of toxicity or evidence of MTD are reported. No evidence of any effect on reproductive parameters. Initially reviewed as unacceptable but upgradeable. (JG, 4/16/86). The submission of # 061666 (see below) does not adequately address the question of diet preparation. The study remains UNACCEPTABLE and is considered not upgradeable since no histopathology was done and the doses are not justified. Gee, 3/3/89.

289- 032 061666 "Diet Preparation Procedures for Studies with Methane Arsonic Acid (MAA)." Supplemental to 041669 - 041674.

TERATOGENICITY, RATS

** 289- 043 088928, "A Teratology Study in Rats with Methanearsonic Acid", (M. Mizens and J.C. Killeen, Jr., Bio/dynamics Inc., Project I.D. Number 89-3456, 9/7/90). Methanearsonic acid (MAA) (purity = 99.73%, Lot #: 107/84) was administered by gavage at concentrations of 0 (vehicle = deionized water), 10, 100, or 500 mg/kg/day during days 6 through 15 of gestation (day 0 = vaginal plug and/or sperm) to 25 mated CD (Sprague-Dawley) rats/group. Another 25 mated female rats received deionized water and served as controls. Maternal NOEL = 10 mg/kg/day (Body weight gain and food consumption were reduced at $\geq$ 100 mg/kg/day. Ano-genital staining and soft stool were increased at 500 mg/kg/day.) Maternal NOAEL = 500 mg/kg/day. Fetal NOEL = 250 mg/kg/day (Reduced fetal weight at 500 mg/kg/day was observed). There was no evidence of teratogenicity. ACCEPTABLE. (Kishiyama & Silva, 1/24/91).

289- 041 086548, "A Teratology Dose Range-Finding Study in Rats with Methanearsonic Acid", (J.S. Chun and J.C. Killeen, Jr., Ricera, Inc., Project I.D. Number 88-0224, December 12, 1989). Methanearsonic acid (MAA) (purity = 99.8%, Lot #: 107/84) was administered by gavage at concentrations of 0 (deionized water), 10, 50, 250, or 500 mg/kg/day during days 6 through 15 of gestation to 8 mated CD (Sprague-Dawley) rats/group (day of mating = day 0 of gestation). MAA was also administered at 0 (deionized water) and 750 mg/kg/day by gavage to 8 mated Sprague-Dawley rats/group/day during days 6 through 19 of gestation (4 extra days administered in error). Maternal NOEL = 10 mg/kg/day (Body weight gain and relative food consumption was reduced at 500 mg/kg. The incidence of soft stool increased at $\geq$ 50 mg/kg. Ano-genital staining was observed at $\geq$ 500 mg/kg. Mortality was excessive (75%) at 750 mg/kg.) Maternal NOAEL = 250 mg/kg/day. Fetal NOEL was not assessable, since fetuses were not examined. These data are supplemental. (Kishiyama & Silva, 1/24/91).

289- 017-022 043228 "Methane Arsonic Acid: Three Generation Reproduction Study in rats." (11/26/1979, Raltech (WARF). MSMA as free acid (MAA) >99%, lot 907-96-301; fed in the diet days 0 - 20 of gestation at 0, 25, 50, 100 or 200 ppm; 20 females per group from F_2a of reproduction study, Record #041669; NOEL > 200 ppm; UNACCEPTABLE, no teratogenic effect reported. MTD not demonstrated, minimal data are presented and an insufficient number of

litters per group are available for evaluation (as low as 13 per group in control and high dose groups). Twenty females in the F_2a parents of the reproduction study were sacrificed on day 20 of gestation with the F_3b litter. The report states "abnormal variations in the rugae of the palate" were found in soft tissue examination but there does not appear to be a treatment-related effect since the high dose and controls were approximately equal in incidence. The number of fetuses with slight hydrocephalus is increased in the high dose but the number of litters (5 each) is comparable to control. In the absence of historical data, the significance of the finding cannot be fully evaluated. The clustering of the effects in 2 high dose litters would indicate some factor other than compound administration as the cause. (Gee and Parker, 4/16/86)

TERATOGENICITY, RABBITS

** 289- 026, 033 050830, 063280 "Methanearsonic Acid Teratology Study in the Rabbit." (Life Science Research, Israel, 3/26/86, report no. PAL/006/ MSM) Methanearsonic acid, technical, 99.8%, batch 107/84; given by oral gavage at 0 (distilled water), 1, 3 or 7 mg/kg/day (5 ml aqueous solution/kg) and at 0 or 12 mg/kg/day to 13-14 rabbits per group, days 7 through 19 of gestation; maternal NOEL = 3 mg/kg/day (reduced weight gain, reduced food consumption), developmental NOEL = 7 mg/kg/day (anomalous number of vertebrae at 12 mg/kg/day. No adverse effect reported. Initially evaluated as unacceptable (no analyses of dosing solutions), but possibly upgradeable. R. A. Marovich, 5/6/87 and Gee, 5/20/87. Supplemental data in Record # 063280 includes records of dosing preparations. The status of this study is upgraded to ACCEPTABLE status with no adverse effect. (Kishiyama & Gee, 3/2/89.)

TERATOGENICITY, HAMSTER

289- 014 011334 (1972, review). No data.

MUTAGENICITY, GNMU

** 289- 042 086549, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with and without Metabolic Activation with Methanearsonic Acid (MAA)", (J.S. Chun and J.C. Killeen Jr., Microbiological Associates Inc., I.D. Number 89-0087, 10/30/89). Methanearsonic acid (MAA, purity 99.8%, Lot #: 107/84) at concentrations of 0 (deionized water), 667, 1000, 3333, 6667, or 10,000 µg/plate was evaluated in Σαλμονελλα τψπηιμυριυμ tester strains TA98, TA100, TA1535, TA1537, and TA1538 with and without rat liver (S-9) homogenate after 48 hours exposure time. MAA did not show any evidence (increased revertants) of mutagenicity in either the initial or confirmatory assay. ACCEPTABLE. (Kishiyama & Silva, 1/25/91.)

** 289- 042 086551, "L5178Y $TK^{+/-}$ Mouse Lymphoma Mutagenesis Assay with Methanearsonic Acid (MAA)", (J.S. Chun and J.C. Killeen Jr., Microbiological Associates Inc., I.D. Number 89-0087, 12/7/89). Methanearsonic acid (MAA, purity = 99.8%, Lot #: 107/84) was used initially in 10 concentrations (triplicate plates) from 300 to 4000 µg/ml (no metabolic activation) or 12 concentrations from 71 to 1688 µg/ml (S9 activation) to evaluate induction of forward mutation in the thymidine kinase locus of mouse lymphoma (L5178Y $TK^{+/-}$ cells. In a repeat assay, 5 concentrations from 2000 to 6000 µg/ml (no metabolic activation) or 6 concentrations from 200 to 950 µg/ml (with S9 activation) were evaluated. Exposure time was 4 hours. Initially, mutation frequency values 0.6 and 0.8 for the 712 and 949 µg/ml groups (+ S9), respectively were statistically greater than control (0.4). In the repeat trial, dosages of $\geq$ 850 µg/ml were too toxic to clone. The mutation frequency for 750 µg/ml, although statistically significantly increased, was not twice that of the solvent control (1.0 vs. 0.7). Based on the equivocal response initially and the lack of reproducibility in the repeat trial, it is concluded MAA is not mutagenic to L5178Y $TK^{+/-}$ cells. ACCEPTABLE. (Kishiyama & Silva, 1/31/91).

289- 014 011334 (1972, review). No data.

289- 016 038109, "Reverse Mutation Assay-Salmonella typhimurium - AEXP-1001 (MSMA)." (10/1975, Microbiological Associates). Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100, letter plus data. UNACCEPTABLE - no protocol or methods are included. Only data are presented indicating no increase in reversion frequency in Salmonella strains at unspecified concentration. (Gee, 3/5/86).

289- 023 041676 "In vivo and in vitro Studies of Selected Pesticides to Evaluate their Potential as Chemical Mutagens." (1977, SRI). MSMA and DSMA; Salmonella strains TA1535, TA1537, TA1538 and TA100, at 0 - 1000 ug/plate, with and without rat liver activation; single plate, single trial; UNACCEPTABLE with no repeat trial, no replicate plates, no justification of maximum concentration and no evidence of cytotoxicity. Inadequate positive controls - not one for each strain. No evidence of increased reversion rate is reported. (Gee, 4/15/86).

289- 024 041677 "Evaluation of Herbicides for Possible Mutagenic Properties." Publication in J. Agr. Food Chem. 20: 649 (1972). Salmonella; UNACCEPTABLE with no adverse effect reported in a review article on 110 herbicides. (Gee, 4/16/86).

MUTAGENICITY, CHROMOSOMES

** 289- 042 086550, "In Vitro Chromosomal Aberration Assay in Chinese Hamster Ovary (CHO) Cells with Methanearsonic Acid (MAA)", (J.S. Chun and J.C. Killeen, Jr., Microbiological Associates Inc., I.D. Number 89-0087, 10/31/89). Methanearsonic acid (MAA, purity = 99.8%, Lot #: 107/84) was used on Chinese hamster ovary cells (CHO-K_1) at 0 (distilled water), 625, 1250, 2500, or 5000 µg/ml and at 1250, 2500, 5000, or 10000 µg/ml with and without an S-9 activation (duplicate flasks, 100 total cells/dose group were scored). Exposure time was 2 (+ S-9) or 8 (no S-9). MAA did not increase the number of chromosomal aberrations. ACCEPTABLE. (Kishiyama & Silva, 1/25/91).

MUTAGENICITY, DNA

** 289- 044 086552, "Unscheduled DNA Synthesis Assay in Rat Primary Hepatocytes with Methanearsonic Acid (MAA)", (J.S. Chun and J.C. Killeen, Microbiological Associates Inc., I.D. Number 89-0087, 10/31/89). Methanearsonic Acid (MAA, purity = 99.8%, Lot #: 107/84) was used at concentrations of 10, 50, 100, 500, 750, or 1000 µg/ml on adult male (Sprague-Dawley) rat primary hepatocytes to assay for DNA damage (autoradiography). Exposure time was 18-20 hours (3 slides/dose were scored, 50 cells/slide). At 1000 µg/ml the dose was too toxic for evaluation. MAA doses in this study did not increase the number nuclear grains observed in either the initial or repeat assays. ACCEPTABLE. (Kishiyama & Silva, 2/5/91).

289- 016 046245 Letter plus data. (10/1/1975, Microbiological Associates.). Cell transformation. MSMA. UNACCEPTABLE with no adverse effect reported. Fischer rat embryo cells infected with Rauscher leukemia virus and Balb/3T3 cells were tested at 0.1, 1 and 10 ug/ml. No details. No transformation was reported. (Gee, 3/5/86).

289- 023 041675 , "In vivo and in vitro Studies of Selected Pesticides to Evaluate their Potential as Chemical Mutagens." (2/1977, SRI). UDS in human embryonic lung fibroblasts, WI-38; MSMA, 58.4% and DSMA; exposed for 1 hour with activation to 10^{-3}, 10^{-4} and 10^{-5} M (3 each) and for 3 hours without activation to 10^{-3} to 10^{-7} M (6 samples each). No increase in the dpm/ug DNA is reported. UNACCEPTABLE but UPGRADEABLE with no adverse effect reported. The report is missing the cell passage number for WI-38, the cytotoxicity and justification of the concentrations selected, the method and quantitation of the recovery of DNA following extraction, the quench correction used for the tritium and the procedure for counting samples by LSC. The use of a 58.4% material as test article and of what the remainder was composed should be explained. (Gee, 4/15/86).

NEUROTOXICITY, HENS

Not required at this time.

SUPPLEMENTARY STUDIES

289- 033 063279 "Methanearsonic Acid (MAA) and Its Salts in Human Gastric Juices - Species Identification with Carbon-13 NMR Spectroscopy." (Raltech Scientific Services, Inc., WI, 5/7/79) Methanearsonic acid and the disodium salt were synthesized with carbon-13 for NMR spectroscopy. Gastric juice from seven patients were compared with aqueous solutions at different pH's and ionic strengths for conversion of the acid form to the monovalent and divalent forms. The average pKa_1 for MAA in gastric juice was 4.05 and the pKa_2 was 8.8. At the pH of 1.46 (the highest of the 7 samples), 99.7 % of MAA was in the acidic form. The study supports the use of the free acid as the testing material by the oral route. SUPPLEMENTAL DATA. Gee, 3/3/89.